PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

CODE	DATE	NTD

ANKOM 11 AUG 2005 GIPO

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FINAL CHECK

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000567	17.02.2005	20.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07F5/02, C07D401/14

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6,8-13
	No:	Claims	7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV.

The separate groups of inventions are:

Group A:
claims 1-7 (synthesis of azole substituted phenylboronic acids)

Group B
claims 8-13 (preparation of oxadiazole coupling products)

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The application claims a general process for the synthesis of azole substituted phenylboronic acids (I), the preferred azole phenylboronic acid of claim 7 and also the Suzuki like coupling of this compound to give protected sulfonamide intermediates (IV). The compound of claim 7 is already known from the cited patent US-B1-6197967. Since this compound is chemically not distinguished over this prior art when prepared according to the methods of the present application, it cannot serve as a "special technical feature" in the sense of Rule 13.2 PCT. That is to say, the skilled person, who was looking for an alternative synthesis of present intermediates (IV) could have started from the known prior art compound. The provision of an alternative synthesis of the said compound (I) is therefore not necessary to provide for the first time the phenylboronic acid intermediate (I). By consequence, the problem underlying the first mentioned invention is the provision of an alternative method to synthesize already known intermediates. The closest prior art is represented by the cited article of Piettre. The solution involves the use of a modified oxadiazole starting product. By contrast, the technical problem of the second invention is the provision of a new intermediate (IV) by way of an analogous Suzuki coupling protocol. The special technical feature of this group resides from the use of a modified coupling partner, which feature is different and not related to the special technical feature of the first invention. In conclusion, both inventions do not share a common technical feature, which would be new and inventive, such that the requirement of unity of invention is not met (Rule 13.1 PCT).

Re Item V.

a) Group A invention
The relevant prior art is represented by D1 (= US-B1-6 197 967) and D2 (= J. MED. CHEM., 40, 1997, 4208-4221 & XP002329872).

Claim 7 has been drafted in terms of a product-by-process claim. In order to be new, the product as such must be new. This is not the case in the light of the disclosure in Table 5 and example 5 of D1. The subject-matter of claim 7 does therefore not appear to have met the novelty requirement of Art. 33(2) PCT. The products of D1 have, however, been obtained by hydrolysing oxadiazole substituted phenylboronic esters. Hence, the process claims are novel over D1. With regard to D2, novelty resides from the structure of present compounds (I) and (II), which do not allow for an aryl residue bonded to the azole moiety. The subject-matter of claims 1-6 does therefore appear to meet Art. 33(2) PCT.

The skilled person, who was looking for an alternative way of synthesizing azole substituted phenylboronic acids would have considered D2, which teaches on pages 4214 and 4216, that phenylboronic acids may be obtained without the need of hydrolysing boronic esters. In the light of the high yields obtainable from the lithiation and boronation of starting azole substituted bromophenyl, we would have arrived at the subject-matter of the present application by merely modifying the oxadiazolo moiety, which does not interfere with the boronic acid synthesis. Starting from D1 as the closest prior art for the azole substituted phenylboronic acid, the skilled person would have recognised that the mentioned modification is not relevant for the synthesis, such that it is not considered to have involved inventive activity. The subject-matter of claims 1-7 does therefore not appear to have met the requirement of Art. 33(3) PCT.

b) Group B invention:
The relevant prior art is represented by D3 (= WO-A-98 40332) and D4 (= WO-A-96 40681). The claimed subject-matter is distinguished over these documents in that the oxadiazole ring is pulled through the entire reaction sequence and at the late stage of deprotected sulfonamide. As such, the novelty requirement of Art. 33(2) PCT has been met. In the light of the fact, that the oxadiazole ring is remote from the reacting coupling

functions, and the necessary oxadiazole substituted phenylboronic acid is available according to prior art synthesis methods, the skilled person would have considered obvious to employ a starting material, which already contained the desired oxadiazole ring. As such, the present modifications are considered to represent an obvious solution of the problem of providing an Suzuki coupling products (IV). Claims 8-13 do not appear to have involved an inventive step in the sense of Art. 33(3) PCT.